IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Randolph J. Noelle et al. Group Art Unit: 1644

Application Serial No. 09/164,568 Examiner: P. Gambel

Filed: October 1, 1998

Title: METHODS FOR INDUCING ANTIGEN-SPECIFIC T CELL TOLERANCE

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REPLY AND AMENDMENTS PURSUANT TO 37 C.F.R. §1.111

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action [Non-Final Rejection] dated October 4, 2000, Applicants submit the following remarks. Reconsideration and re-examination of the subject application, pursuant to and consistent with 37 C.F.R. 1.112, and in light of the remarks which follow, are respectfully requested.

Turning now to the Official Action, the previous election of "autoantigen" is confirmed. The objection to the Information Disclosure Statement is noted. An Information Disclosure Statement citing references known to Applicants is submitted herewith.

Claims 54-63 stand rejected under 35 U.S.C. §112, first paragraph, as being non-enabled. Essentially, the position of the Examiner is that the specification does not adequately enable a method of inducing tolerance to an autoantigen. The Examiner asserts that it is unpredictable to intervene in an established autoimmune response. Also, the Examiner suggests that in view of this unpredictability, there is no nexus between the disclosed in vitro result and in vivo efficacy. Further, the Examiner cites publications in alleged support of the enablement rejection. These issues are addressed below.

Essentially, the Examiner alleges that the specification contains insufficient evidence to substantiate that the subject humanized anti-gp39 antibody can be used to intervene in a autoimmune disease. This rejection is respectfully traversed.

At the outset, it is noted that the Examiner cites Biogen press releases concerning the stopping of clinical trials relating to a particular 5C8 antibody in support of the rejection. Particularly, it is indicated that this antibody has been shown to cause undesired hemolytic events (stroke). Applicants respectfully advise that IDEC's antibody is currently in clinical

trials for multiple sclerosis and previously for lupus. No adverse safety issues have been observed. Accordingly, Biogen's problems are irrelevant to the subject claims which are directed to use of a different anti-gp39 antibody.

Secondly, the Examiner alleges unpredictability with treating an ongoing autoimmune disease and cites various supporting documents (Stuber et al., Corey et al., Restekovic et al. and Biacome et al.). However, Applicants respectfully submit that this rejection is unsubstantiated as it is wholly inconsistent with the same Examiner's disposition of another application, U.S. Serial No. 09/223,634. Particularly, in that application, the Examiner allowed generic claims directed to treatment of any T cell mediated autoimmune disorder using an anti-gp39 antibody or fragment, soluble CD40 or soluble CD40 fusion protein.

It is conjectured that the Examiner has maintained the enablement rejection because the evidence submitted in the above-identified, now-allowed application is not of record herein. Accordingly, for the Examiner's convenience, Applicants provide the information submitted therein.

Particularly, Applicants refers to the data submitting during prosecution of the earlier Applicants relating to EAE. Applicants submitted, during prosecution of the parent application, now issued, data in the chronic EAE model as well as the relapse model, which demonstrated that administration of an antibody to CD40 ligand provided an effective means for intervening in the disease process. Also, Applicants attachs to this reply an article by Howard et al. [Journal in *Clinical Investigation*, Vol 103, No. 2 (January 1999) pp. 281-290] which shows that the administration of anti-CD40 ligand antibody in a relapsing EAE animal model severely inhibited disease induction, myelin peptide-specific delayed-type hypersensitivity responses, and the induction of encephalitogenic, effector cells, as well as impairing the expression of clinical disease in recipients of encephalitogenic T-cells. In fact, data suggests that CD40-CD40 ligand interactions are involved in directing the CNS migration of such cells, and that the blockade of CD40 ligand – CD40 interactions has application in an immunotherapeutic strategy for treating ongoing T-cell mediated autoimmune diseases.

Also, Applicants further attaches to this Reply information from a grant by the inventor, which presents yet additional data in another EAE model. In particular, the Examiner is respectfully referred to the preliminary studies referred to at pages 18 and 19,

which discuss that the administration of anti-CD40 ligand inhibited the onset of PLP-EAE in SJL/j. mice, and that treatment at the disease onset causes a significant decrease of clinical symptoms compared to control mice, and that even after encephalitogenic T-cells are present, that the administration of antibody to CD40 ligand can interfere with the effector phase of the disease.

Also, at page 19, the inventor discusses the basis for the therapeutic effect of anti-CD40 ligand during priming. Specifically, he explained that, during the priming phase of EAE, their results are consistent with the fact that anti-CD40 ligand prevents the differentiation of T-cells to an inflammatory *in vivo* type, which blocks IL-2 production. Also, the data obtained further suggests that treatment with antibody to CD40 ligand inhibits disease onset, by changing the effector properties of MOG-reactive T-cells, and that anti-CD40 ligand therapy inhibits Th_1 development and the ability of T-cells to cross the blood brain barrier. Still further, it is discussed therein that treatment with an antibody to CD40 ligand in animals with established EAE resulted in a reduction of clinical symptoms.

Additionally, Applicants further attaches to this Reply, for the Examiner's review, a brief overview of phase I clinical results obtained in a human MS clinical trial being conducted at Dartmouth. It should be noted that all patients in the study have demonstrated stabilization or improvement of their EDSS scores. This is believed to provide further support of the efficacy of the claimed method.

Also, the Applicants respectfully refers the Examiner to information attached hereto relating to the treatment or intervention inflammatory bowel disease or chronic experimental colitis. Specifically, the Examiners is referred to the article entitled "Chronic and Experimental Colitis is Dependent on the CD154/CD40 Pathway and Can be Intervened by Anti-CD154 Administration". This reference contains experimental data substantiating treatment of mice in an accepted animal model of IBD with anti-CD40L antibody substantially impaired disease progression.

Further, Applicants respectfully refer to Liu et al., *Journal of Immunology*, Vol. 163 (1999) pp. 4049-4057, which studies the hyper expression of CD40 ligand in inflammatory bowel disease, and teaches that it contributes to pathogenic cytokine production. It should be noted that the authors conclude based on their findings, that CD40 ligand regulation is involved in pathogenic cytokine production which is significant to inflammatory bowel

disease, and that blockade of CD40-CD40 ligand interaction may have therapeutic benefits for treating such patients.

Further, the article contains information which shows that the addition of a blocking monoclonal antibody to specific to CD40 ligand or CD40 in cultures comprising freshly isolated lamina propria T-cells obtained from patients with inflammatory bowel disease significantly decreased monocyte IL-2 and TNF production, both of which cytokines are involved in the disease process.

Still further, Stuberg et al., *Journal of Experimental Medicine*, Vol. 183 (1996) pp. 693-698, similarly describes that blocking of the CD40 ligand-CD40 interactions in yet another experimental model for a Th_1 mediated disease, *i.e.*, inflammatory colitis, particularly during the induction phase of the Th_1 response, prevented cytokine production by lamina propria CD40 positive T-cells.

Also, in further support of the generic efficacy of the invention for treating autoimmune disorders, Applicants respectfully refers to yet another article [Blosa et al., *Journal of Immunology*, Vol. 159 (1997) pp. 4620-4627] which discloses that CD40 ligand/CD40 interactions are necessary for the initiation of insulitis and diabetes in NOD mice, which comprise an accepted animal model for type 1 diabetes. This article shows that the administration of an antibody to CD40 ligand prevented insulitis by inhibiting the development and further accumulation of pathogenic Th_1 cells. While the subject claims are directed to treatment, not prevention of T-cell autoimmune diseases, the inventor noted during the recent interview that the methods and reagents suitable for intervening early in type 1 diabetes, are being developed. In particular, this is evidenced by an article by Flanders et al., *Autoimmunity*, Vol. 29, No. 3 (1999) pp. 235-246, also attached to this Reply, which describes that an alternative approach to prevention of type 1 diabetes may include a vaccine in early childhood to induce tolerance to critical auto antigens. Also, this reference reviews the status of current diabetes prevention trials in humans and reports that new intervention strategies are being currently tested in animal models. Based on this information, and the Stuberg et al. article, it is reasonable to conclude that administration of an antibody to CD40 ligand as well as other gp39 antagonists will provide an effective means for intervening in type 1 diabetes, particularly early on in the disease process.

Finally, the inventor also referred to recent experimental data in an animal model for oophoritis, which shows that the administration of antibodies to CD40 ligand (MR-1) blocks the transfer. Specifically, Applicants further attaches to this Reply data which shows that MR-1 administration blocked the transfer of disease by T-cells for D3TX mice, and that MR-1 inhibited the disease and autoimmunity in D3TX mice. This data is also attached to Applicants's Reply. Based on the foregoing, and as agreed by the Examiner at the recent interview, withdrawal of the outstanding 112 scope of enablement rejections is respectfully requested.

Further, the Examiner's rejection is inconsistent with his recent suspension of an application, U.S. Serial No. 09/223,634, that is directed to treating T cell mediated autoimmune diseases using a gp39 antibody.

Also, Applicants respectfully submit that the enablement rejection is inconsistent with the same Examiner's allowance of U.S. Patent 5,993,816, which patent contains broad claims directed to inhibiting humoral immune responses using an anti-gp39 antibody, wherein such inhibition can be in vitro or in vivo. Applicants respectfully submit that it would be clearly understood that such inhibition would be therapeutically beneficial in the context of B cell mediated autoimmune diseases. Therefore, the Examiner has previously conceded that gp39 antagonists, and particularly anti-gp39 antibodies, have therapeutic application both in the treatment of B and T cell mediated autoimmune diseases.

Thus, Applicants respectfully submit that the subject claims should be passed to issue.

Also, Claims 54-63 stand rejected under 35 U.S.C. §112, first paragraph, as not being adequately described. This rejection is respectfully traversed.

Essentially, for this rejection, the position of the Examiner is that the invention is not adequately described as the invention requires knowledge of a specific antigen that elicits an autoimmune response. Thus, the Examiner suggests that Applicants were not in possession of the general invention, as such antigens are not characterized. However, this is submitted to be improper.

Contrary to the rejection, possession of the invention does not require knowledge or isolation of specific autoantigens. Rather, what is required is a knowledge of the types of cells that elicit autoimmunity.

For example, in the context of autoimmune diabetes, a subject develops an autoimmune response against pancreatic islet cells. In another autoimmune disease, multiple sclerosis, a subject develops autoimmune responses against myelin expressing cells. Similarly, for another autoimmune disease, IBD, the subject develops an autoimmune response against cells in the bowel. Analogously, in ooploritis, the subject develops an autoimmune response against certain reproductive cells.

Thus, with this knowledge, there is sufficient information to practice the invention. For example, in the context of diabetes, treatment would involve co-administration of islet cells and a gp39 antagonist. Analogously, for other autoimmune diseases, one skilled in the art would be able, in most instances, to select appropriate host cells that elicit the autoimmune response. Consequently, such methods would similarly entail co-administration of such cells with a gp39 antagonist. It does not require a knowledge of the specific autoantigen(s), or even that they be in isolated form.

Therefore, based on the foregoing, Applicants respectfully submit that the invention is adequately described in the disclosure, particularly as the asserted basis for inadequate description is not germane to the claimed invention. Indeed, the invention can be practiced without knowledge or isolation of particular autoantigens. Instead, the invention merely requires knowledge of the types of cells that elicit autoimmunity which was well known at the time of invention in the context of a number of different autoimmune diseases.

In view of the foregoing, the application is now believed to be in form for allowance, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

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By: _____

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